

25-10-2001

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

 KOLSTER OY AB
 Iso Roobertinkatu 23
 P.O. Box 148
 FIN-00121 Helsinki
 FINLANDE

Date of mailing (day/month/year) 11 October 2001 (11.10.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2980578PC/su	
International application No. PCT/FI00/00140	International filing date (day/month/year) 22 February 2000 (22.02.00)

1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address ANCIBIO LTD. 375 West Regent Street Glasgow G2 4LH United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person
 ☐ the name
 ☒ the address
 ☒ the nationality
 ☒ the residence

Name and Address LICENTIA OY Erottajankatu 19 B FIN-00130 Helsinki Finland	State of Nationality FI	State of Residence FI
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

CORRECTED
VERSION

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned
☐ the International Searching Authority
 ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority
 ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Céline Faust <i>Celine Faust</i> Telephone No.: (41-22) 338.83.38
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PCT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

KOLSTER OY AB
Iso Roobertinkatu 23
P.O. Box 148
FIN-00121 Helsinki
FINLANDE

Date of mailing (day/month/year) 27 août 2001 (27.08.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2980578PC/su	
International application No. PCT/FI00/00140	International filing date (day/month/year) 22 février 2000 (22.02.00)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address ANCOBIO LTD. 375 West Regent Street Glasgow G2 4LH United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address LICENTIA OY Erottajankatu 19 B FIN-00130 Helsinki United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Jean-Marie MCADAMS Telephone No.: (41-22) 338.83.38
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FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
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CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
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CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

(1) A result falling into Class II is an indicator of a specific type of male factor infertility, associated with *POLG* dysfunction. This genotype is never found in fertile males. Other clinical or biochemical investigations of both partners can essentially be dispensed with as unnecessary. Even in the absence of sperm quality data, it indicates that intra-uterine insemination and probably IVF are likely to fail, and that recourse to ICSI (intra-cytoplasmic sperm injection) is advisable.

(2) A result falling into Class I does not exclude male factor infertility of other types, nor any other diagnosis.

(3) A result falling into Class III is ambiguous, and warrants further genetic investigation of the *POLG* locus, as illustrated below (example 2).

Example 2

Complete analysis of the *POLG* gene as a diagnostic test for male infertility

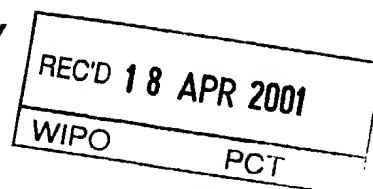
Results from the type of analysis illustrated in Example 1 are necessarily ambiguous in the case of individuals who prove to be heterozygous at the *POLG* gene CAG repeat (i.e. who possess one copy of the wild-type, 10-repeat allele, plus one copy of some other length variant). In these cases, further investigation is warranted, in order to establish whether they represent cases of true heterozygotes (one fully functional, one mutant copy of the gene), as found amongst fertile males and controls, or whether they represent compound heterozygotes carrying one copy of the gene mutated within the *POLG* CAG repeat tract, and a second copy which has a pathological mutation elsewhere in the gene. The present invention thus covers not only the use of genotyping at the CAG repeat, but also the complete sequencing of the *POLG* gene as a diagnostic procedure for the determination of male infertility associated with *POLG* gene dysfunction, in cases where genotyping at the CAG repeat is insufficient to permit an unambiguous molecular diagnosis. Because such cases are expected to constitute up to half of all individuals with *POLG*-associated infertility, based on the observed frequencies of homo- and heterozygotes, i.e. given the excess number of heterozygotes amongst the infertiles, the further analysis illustrated in this Example will have an important diagnostic value, as regards the counselling and treatment to be offered.

DNA is prepared from the same sources and using the same methods as indicated under Example 1 (above). Long-extension PCR is carried out using a series of primer pairs flanking blocks of exons of the *POLG* gene, as

illustrated in Figure 3, creating products that include the entire coding region of the gene, the 5' and 3' untranslated segments of the *POLG* mRNA, the proximal promoter of the gene, and all intron/exon boundaries. Oligonucleotide primers are based on the publicly available sequence of the *POLG* gene (deposited in the Genbank database as accession number AC005317), and sourced from companies such as indicated under Example 1. In this specific example, illustrated in Figure 2, the relevant segments of the *POLG* gene are amplified initially as 3 large PCR products, although many other strategies are equivalent, based on other combinations of primers according to the database sequence. LX-PCR is carried out with a standard reagent kit (e.g. Boehringer Mannheim Extend DNA Polymerase) under manufacturer's recommended conditions or using equivalent materials sourced elsewhere. PCR products are analysed by agarose gel electrophoresis and purified from agarose gels by standard, spin-column methods, e.g. using kits available from Qiagen or similar manufacturers. A total of 52 sequencing primers are also required (one in each direction for the 21 short exons and boundaries, two in each direction to cover the longer exon 23, and three in each direction to cover the longest exon, exon 2, in which the CAG repeat lies, presenting additional difficulties. The 20 bp sequences of these correspond with intronic sequences located approximately 30 bp up- and downstream of the various intron-exon boundaries, based on the database-deposited gene sequence. In addition, internal exonic sequencing primers (one for each strand) are required for 20 bp regions in the middle of exon 23 and exon 2, as well as 20 bp on either side of the CAG repeat (one strand only, in each case, reading towards the repeat).

Fluorescent DNA sequencing is carried out using a standard dye-terminator reagent kit (e.g. PerkinElmer Big Dye) in thermal cycling reactions using the long PCR products as template and each sequencing primer as appropriate under the kit manufacturer's recommended conditions. Sequencing reaction products are analyzed by gel or capillary electrophoresis, on a suitable electrophoresis/fluorescent analysis instrument, e.g. ABI 310 Genetic Analyzer (PerkinElmer), using the manufacturer's data collection and analysis software.

DNA sequences are carefully examined for evidence of 3 types of detectable heterozygosity, which manifest differently on the sequence traces, as follows. (a) A heterozygous point mutation manifests as a specific ambiguity localized to one nucleotide pair and detectable on both strands in a congruent



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference 2980578PC/su	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FI00/00140	International filing date (day/month/year) 22/02/2000	Priority date (day/month/year) 22/02/1999	
International Patent Classification (IPC) or national classification and IPC C12Q1/00			
Applicant ANCOBIO LTD et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 20/09/2000	Date of completion of this report 11.04.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Maucher, C Telephone No. +49 89 2399 7415



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/FI00/00140

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-14,17-19	as originally filed	
15,16	with telefax of	09/05/2000

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/1 as originally filed

Sequence listing part of the description, pages:

1-5, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/FI00/00140

listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 14.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 14.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/FI00/00140

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims 1-13
	No: Claims
Inventive step (IS)	Yes: Claims 1-12
	No: Claims 13
Industrial applicability (IA)	Yes: Claims 1-13
	No: Claims

**2. Citations and explanations
see separate sheet**

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/FI00/00140

Point I:

1. The amended pages 15-16 meet the requirements of Article 34(2)(b) PCT.

Point II:

The priority of present claims 1-13 is valid. The intermediate document "EUROPEAN JOURNAL OF HUMAN GENETICS, vol. 7, pages 140-146" is assumed to having been published on 17.3.1999, i.e. between the priority date and the filing date of the present application. Therefore, said document was not taken into account for examination of novelty and inventive step of present claims 1-13.

Point III:

Claim 14 was not examined, since it has not been searched.

Point V:

Reference is made to the following documents:

- D1: HUMAN REPRODUCTION,
vol. 3, no. 1, 1998, pages 51-61
- D2: CLINICAL CHEMISTRY,
vol. 44, no. 8, 1998, pages 1616-1620
- D3: GENOMICS,
vol. 36, 1996, pages 449-458

D1 describes diagnostic tools in male infertility (title). Mitochondrial mutations are correlated with male infertility (p 56, r col to p 57, l col).
The POLG gene is not mentioned.

D2 discloses a correlation of sperm motility with mitochondrial enzymatic activity (title).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/FI00/00140

POLG gene is not mentioned.

D3 discloses the characterization of POLG gene (abstract). Instability of a repeat region is mentioned (p 455, r col, 2nd par to p 456, l col, 1st par).

Infertility is not mentioned in said article.

1. The subject-matter of **claims 1-12** appears to be **novel and inventive** (Articles 33(2) and (3) PCT), since none of the available prior art documents, either if taken alone or in any combination, discloses the relationship of POLG gene mutations with male infertility and its use in detection of infertility.
2. The subject-matter of **claim 13 is formally novel**, since D3 does not disclose a kit.

However, it is not considered inventive to assemble reagents in a kit for the identification of presence or absence of mutation in the POLG gene, i.e. for instance the length of the CAG repeats, in the light of D3: D3 already discloses a method and reagents for the assessment of stability and size fluctuation of the CAG repeats (p 450, r col, last full par and p 455, r col, 1st full par).

Thus, the subject-matter of **claim 13 is not considered to meet the requirements of Article 33(3) PCT**.

Point VIII:

Independent claim 13 does not meet the requirements of Article 6 PCT, in that the matter for which protection is sought is not clearly defined. The claim attempts to define the diagnostic kit of interest in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result have not been added (see Point V, 2. above).

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 30 October 2000 (30.10.00)	
International application No. PCT/FI00/00140	Applicant's or agent's file reference 2980578PC/su
International filing date (day/month/year) 22 February 2000 (22.02.00)	Priority date (day/month/year) 22 February 1999 (22.02.99)
Applicant JACOBS, Howard et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 20 September 2000 (20.09.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Charlotte ENGER

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2980578PC/su	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/FI 00/00140	International filing date (<i>day/month/year</i>) 22 February 2000	(Earliest) Priority Date (<i>day/month/year</i>) 22 February 1999
Applicant Acobio Ltd et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (See Box I).

2. ☐ Unity of invention is lacking (See Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

- ☒ filed with the international application.
- ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
- ☐ transcribed by this Authority.

4. With regard to the title, ☐ the text is approved as submitted by the applicant.
☒ the text has been established by this Authority to read as follows:
 Diagnostic and screening method for male infertility

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

- Figure No. _____
- ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
- ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI00/00140

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: **14**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The Claims or the description does not disclose how the pathological conditions of claim 14 is associated with or related to male infertility I.e. the claim does not comply with PCT article 6 and has not been searched.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/00140

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/48 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROVIA A ET AL: "Analysis of the trinucleotide CAG repeat from the human mitochondrial DNA polymerase gene in healthy and diseased individuals" EUROPEAN JOURNAL OF HUMAN GENETICS, vol. 7, 1999, pages 140-146, XP002901094 the whole document --- -/--	1-13

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 June 2000

Date of mailing of the international search report

28 AUG 2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

P. Andersson/Eö

INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/00140

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE DIALOG INFORM SERVICES [Online] file 34; BARRATT CLR ET AL: "Diagnostic tools in male infertility" retrieved from DIALOG, accession no. 06789473, SciSearch acc. no. Genuine Art.: ZR801 XP002901095 abstract & HUMAN REPRODUCTION, vol. 3, no. 1, April 1998 (1998-04), pages 51-61, ---	1-13
A	DATABASE DIALOG INFORMATION SERV. [Online] File 34, SciSearch(R); RUIZPESINI E ET AL: "Correlation of sperm motility with mitochondrial enzymatic activities" retrieved from DIALOG INF.SERV., accession no. 06953993/25; Genuine Art. 107QW XP002901096 abstract the whole document & CLINICAL CHEMISTRY, vol. 44, no. 8, August 1998 (1998-08), pages 1616-1620, ---	1-13
A	ROPP PH A ET AL: "Cloning and characterization of the human mitochondrial DNA polymerase, DNA polymerase gamma" GENOMICS, vol. 36, 1996, pages 449-458, XP002901097 the whole document -----	1-13